REMARKS

Further and favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Entry of the amendments is proper under 37 CFR §1.116, because the amendments place the application in condition for allowance and do not raise any new issue requiring further search and/or consideration. The amendments are necessary and were not earlier presented, because they are made in response to arguments raised in the final rejection. Entry of the amendments is thus respectfully requested.

Claims 1, 3, 5-7 and 9-11 were pending in this application when examined.

Claim 1 has been amended to limit the "organic amine" to "aminomethylsulfonic acid and aminoethylsulfonic acid". As a result, claim 10 has been amended to recite "wherein the concentration of the organic amine is 0.05 to 5w/v%", and claim 11 has been amended to depend from claim 1.

Claims 5-7 and 9 have been cancelled without prejudice or disclaimer.

I. The Characteristics of the Presently Claimed Invention

The method for treating inflammatory disease of the external segment or the anterior segment of the eye of amended claim 1 includes the following features:

(I) administering to the eye an aqueous eye drop comprising:

(1) 2-amino-3-(4-bromobenzoyl)phenylacetic acid ("bromfenac") or its pharmacologically acceptable salt or a hydrate thereof, and

(2) at least one organic amine selected from the group consisting of aminomethylsulfonic acid and aminoethylsulfonic acid,

(3) once a day, and

(II) maintaining a therapeutically effective concentration of 2-amino-3-(4-bromobenzoyl)phenylacetic acid in the anterior aqueous humor of the eye.

The eye drops used in the presently claimed method unexpectedly maintain an excellent therapeutically effective concentration of bromfenac in the anterior aqueous humor of the eye, and thus treat inflammatory disease of the eye. The intraocular penetration of bromfenac in the claimed method is caused by the interaction between bromfenac and aminomethylsulfonic acid or aminoethylsulfonic acid.

Experimental Example 1 (Formulation 3) and Experimental Example 2 (Formulations 5 and 6) on page 20, line 2 to page 26, line 2 of the specification clearly demonstrate the unexpected effects of the presently claimed invention.

In Formulation 3, 0.2 g of aminoethylsulfonic acid is used relative to 0.1 g of bromfenac 3/2 hydrate; in Formulation 5, 0.5 g of aminoethylsulfonic acid is used relative to 0.1 g of bromfenac 3/2 hydrate; and in Formulation 6, 1.0 g of aminoethylsulfonic acid is used relative to 0.1 g of bromfenac 3/2 hydrate (see Tables 1 and 4 on pages 20 and 24, respectively).

Table 3 on page 23 shows that the concentration of bromfenac in the aqueous humor 2 hours after the intraocular administration increased about 1.6 times (350/214) in Formulation 3 as compared to the eye drops of Formulation 1.

Furthermore, Table 5 shows that 24 hours after the puncture, the inhibition rate of Formulation 5 was 25.5%, the inhibition rate of Formulation 6 was 73.9%, and the inhibition rate of the Formulation 4 (where no aminosulfonic acid was added) was only 0.3% (see page 26).

Accordingly, it is clear from Tables 3 and 5 that the administration of bromfenac and aminomethylsulfonic acid and/or aminoethylsulfonic acid once per day unexpectedly maintains a superior therapeutically effective concentration of bromfenac in the anterior aqueous humor of the eye.

II. Claim Rejections Under 35 U.S.C. § 103

A. Ogawa et al. in view of Kessler

The Examiner rejects claims 1, 3, 6, 7 and 9-11 under 35 U.S.C. 103(a) as being unpatentable over Ogawa et al. (U.S. 4,910,225) in view of Kessler (U.S. 5,849,291). As applied to the amended claims, Applicants respectfully traverse the rejection.

As discussed above, the method of claim 1 includes the feature of administering "at least one organic amine selected from the group consisting of aminomethylsulfonic acid and aminoethylsulfonic acid".

Ogawa et al. describe an ophthalmic composition for inflammatory eye disease, which comprises a sodium salt of bromfenac. However, the reference does not disclose or suggest aminomethylsulfonic acid or aminoethylsulfonic acid, and Kessler does not remedy these deficiencies.

Therefore, claim 1 would not have been obvious over Ogawa et al. in view of Kessler.

Claims 3, 10 and 11 depend from claim 1, and thus also would not have been obvious over the references.

Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

B. Ogawa et al. in view of Kato et al.

The Examiner rejects claims 1, 3, 10 and 11 under 35 U.S.C. 103(a) as being unpatentable over Ogawa et al. in view of Kato et al. (U.S. 5,945,121). As applied to the amended claims, Applicants respectfully traverse the rejection.

The method of claim 1 includes the features of administering to the eye an aqueous eye drop "**once per day,** and maintaining a therapeutically effective concentration" of bromfenac.

Test example 1 of Kato et al., shows the retentivity of liposome eye drops on the corneal surface of the eye for 30 minutes after topical application of eye drops containing taurine. In Test example 2, Kato et al. teach that the eye drops were repeatedly applied **4 times per day** for 5 days (see col. 29, lines 64-67).

It would not have been obvious to a person of ordinary skill in the art that the efficacy of a medicine could be maintained for a long term of 24 hours, as in the presently claimed method, from the teaching of Kato et al. of repeatedly applying the eye drops 4 times per day for 5 days. Moreover, even if taurine were included in a bromfenac-containing eye drop, based upon Kato et al.'s teaching of repeatedly applying the eye drops 4 times per day for 5 days, the claimed method of administering to the eye an aqueous eye drop "**once per day,** and maintaining a therapeutically effective concentration" of bromfenac would not have been obvious over the references.

Furthermore, Ogawa et al. teach that "[i]n the form of eye drops, one to several drops per dose are instilled with a frequency of once to **4 times a day** according to the clinical condition" (emphasis added) (see col. 4, lines 51-53).

In Experimental Example 2 of the present specification, the inhibition rate (%) of Formulation 4, which does not include any aminosulfonic acid, is **0.3%.** It is clear that the experimental model used in Experimental Example 2 is a model suffering from a serious disease wherein the administration of eye drops only once per day is not enough. However, in the models suffering from a serious disease, a superior and unexpected result of an inhibition rate of **25.5% and 73.9%** (85 or 246 times) can be achieved by administering the compositions of Formulation 5 or 6. Thus, the specification shows that even a serious disease can be treated by administering the eye drops of the method of claim 1 only once per day.

Accordingly, it would not have been obvious or even conceivable to a person of ordinary skill in the art that the eye drops in the claimed method could maintain a therapeutically effective concentration for a long period of time of 24 hours, even if taurine, as described in Kato et al., were applied to bromfenac, as disclosed in Ogawa et al. Thus, even an eye disease which would normally require the administration of eye drops several times a day may be treated by the claimed method of administering an aqueous eye drop once a day, as the eye drops in the claimed method have enhanced retentivity.

Therefore, the method of claim 1 would not have been obvious over the references.

Claims 3, 10 and 11 depend from claim 1, and thus also would not have been obvious over the references.

Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

C. Miyagi et al. in view of Ogawa 2

The Examiner rejects claims 1, 3, 6, 7, 9 and 10 under 35 U.S.C. 103(a) as being unpatentable over Miyagi et al. (U.S. 6,281,224) in view of Ogawa et al. (Effects of Bromfenac Sodium, Nonsteroidal Anti-Inflammatory Drug, on Acute Ocular Inflammation, hereinafter "Ogawa 2"). As applied to the amended claims, Applicants respectfully traverse the rejection.

Miyagi et al. describe a pranoprofen ophthalmic solution containing an organic amine. In the reference, the solution is stabilized by combining pranoprofen with an organic amine (trometamol). The Examiner cites Ogawa 2 for disclosing that bromfenac is more potent than pronoprofen.

Proranon® ophthalmic solution 0.1% contains pranoprofen and trometamol and is commercially available in Japan (see Proranon® ophthalmic solution 0.1% and partial English translation, enclosed). The Proranon® translation discloses that 1-2 eye drops are administered **four times a day** (see "[Use/Dose]"). Thus, a person of ordinary skill in the art would not consider pranoprofen to inhibit the inflammation of the eye for 24 hours after administration only once a day.

Accordingly, even if bromfenac were to replace pranoprofen in the Proranon®, one of ordinary skill in the art would not have had any reasonable expectation of success of treating inflammatory disease of the eye by administering the composition only once a day, because the Proranon® translation teaches 1-2 eye drops are administered four times a day.

Therefore, one of ordinary skill in the art would have had no reasonable expectation of success of arriving at the claimed method, which includes the feature of administering to the eye an aqueous eye drop **once per day,** and maintaining a therapeutically effective concentration of bromfenac, from the disclosures of Miyagi et al. and Ogawa 2.

Thus, claim 1 would not have been obvious over the references.

Claims 3 and 10 depend directly from claim 1, and thus also would not have been obvious over the references.

Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

III. Conclusion

For these reasons, Applicants take the position that the presently claimed invention is clearly patentable over the applied references.

Therefore, in view of the foregoing amendments and remarks, it is submitted that the rejections set forth by the Examiner have been overcome, and that the application is in condition for allowance. Such allowance is solicited.

Respectfully submitted,

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